Statins Evaluation in Coronary procedUres and REvascularization Trial (SECURE-PCI)

A RANDOMIZED, MULTICENTER CLINICAL TRIAL TO ASSESS THE EFFECT OF ATORVASTATIN IN PATIENTS WITH ACUTE CORONARY SYNDROME AND INTENDED PERCUTANEOUS CORONARY INTERVENTION

Study Design:	Randomized
Diagnosis:	Acute Coronary Syndrome with planned coronary percutaneous intervention
Steering Committee:	Dr. Otávio Berwanger (Co-chair) Dr. Renato Delascio Lopes (Co-chair) Dr Luiz Alberto Mattos Dr. Alexandre Biasi Cavalcanti Dr. Pedro G. M. de Barros e Silva Dr. Hélio Penna Guimarães Dr. Amanda Sousa Dr. José Eduardo Sousa Dr. Roberto Giraldez Dr. Christopher B. Granger Dr. John H. Alexander
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Protocol Version	6.0
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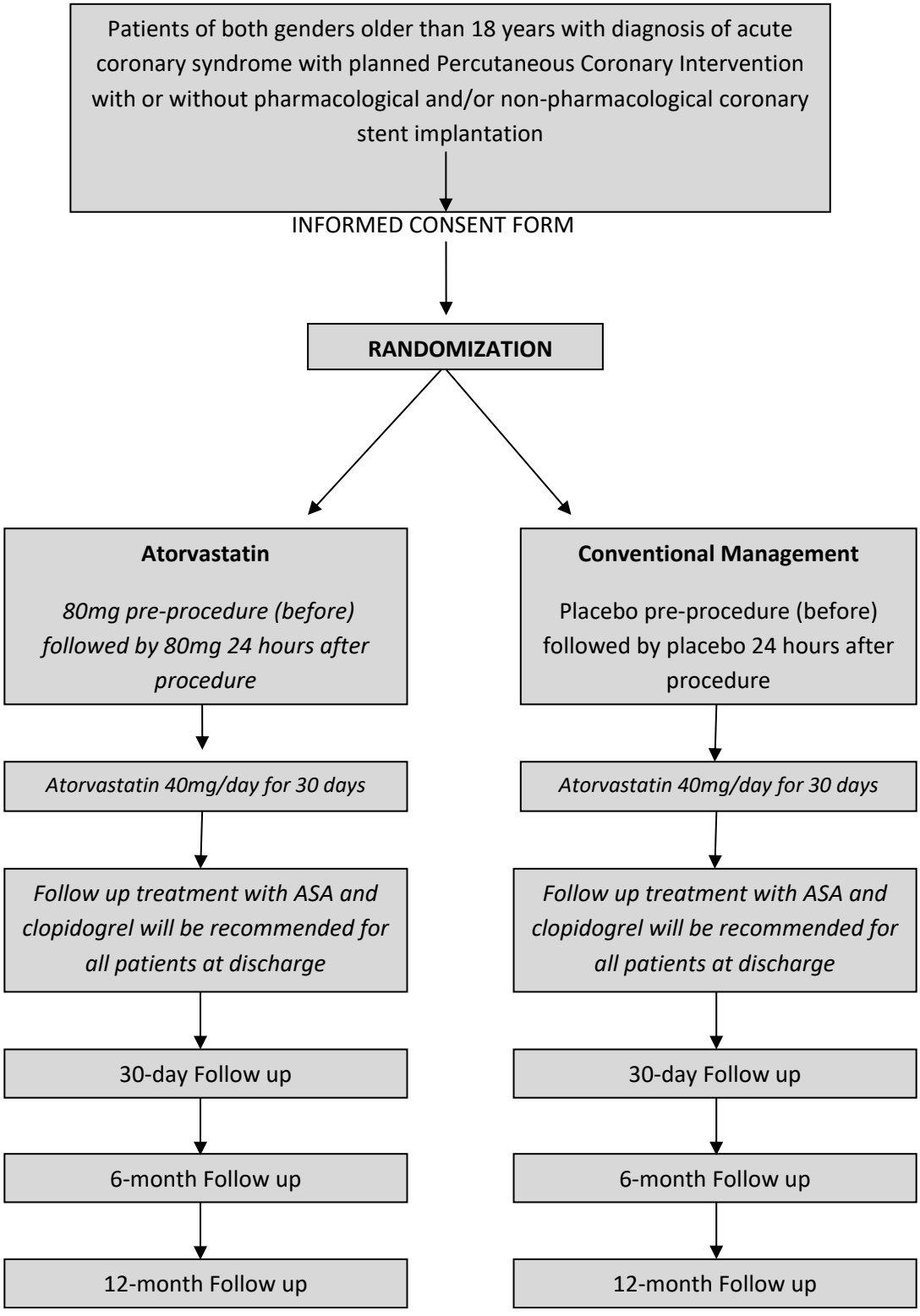
SECURE-PCI Study Flowchart



Title	**SECURE-PCI Study** Statins Evaluation in Coronary procedUres and REvascularization Trial – Percutaneous Coronary Intervention
Project Offices	Research Institute – RI - HCOR Abílio Soares Street, 250 Zip Code 04005-000 - São Paulo – SP – BRAZIL Brazilian Clinical Research Institute (BCRI) Pedro de Toledo Street, 314, Vila Clementino, Zip Code: 04039-000 - São Paulo – SP – Brazil, Phone: +55 11 5904 7339 Fax: +55 11 5904 7331
Co-Chairs	Otavio Berwanger and Renato Delascio Lopes
Steering Committee	Otavio Berwanger, Renato Delascio Lopes, Luiz Alberto Mattos, Alexandre Biasi Cavalcanti, Pedro G. M. de Barros e Silva, Hélio Penna Guimarães, Amanda Sousa, José Eduardo Sousa, Roberto Giraldez, Christopher B. Granger, John H. Alexander
Study Sample Size/number of sites	75 sites in Brazil (ACT network + SBHCI members) – competitive recruitment
Study Design	Randomized clinical trial, multicenter, national, pragmatic, blinded outcome assessment
Methodological Quality	Concealed randomization (by web) Blinded Outcome Evaluators Committee Intention to treat analysis.
Primary Outcome	MACE incidence (total mortality, non-fatal MI, non-fatal stroke or coronary revascularization in 30 days)
Secondary Outcomes	Individual components of primary outcome over 30 days, 6 months and 1 year Cardiovascular mortality at 30 days, 6 months and 1 year Stent thrombosis at 30 days, 6 months and 1 year Target vessel revascularization at 30 days, 6 months and 1 year MACE incidence at 6 and 12 months Coronary revascularization
Inclusion Criteria	Male and female patients (age > 18 years) with Acute Coronary Syndrome diagnosis according to standardized criteria with planned percutaneous coronary intervention with or without pharmacological and/or conventional coronary stent implantation
Key Exclusion Criteria	Pregnancy or women of childbearing potential not using an effective contraceptive method Absolute contraindications to statin use Use of any statin at the maximum dose in the last 24 hours Fibrate usage in the last 24 hours before percutaneous coronary intervention

Sample size estimation	Considering a primary outcome rate of 12.3% at 30 days, a relative risk reduction of 25%, for a 90% power and a two-tailed alpha of 5%, it would be necessary to include at least 4192 patients.
Treatment Plan	Atorvastatin 80mg pre-procedural (before) followed by 80mg 24 hours post-procedural versus conventional management. After that, all patients will receive atorvastatin 40mg/daily for 30 days. Patients that for any reason had been randomized and have not undergone and will not undergo angioplasty will be followed by the intention to treat analysis principle; however the study drug (loading and/or booster dose, as well as maintenance doses) and the statin prescription to this patient will be at the responsible investigator discretion (recommended in cases of angiography with coronary artery disease evidence).
Co-interventions	Concomitant treatment with ASA and clopidogrel will be recommended for all patients at discharge.

SUMMARY

ACRONYMS AND ABBREVIATIONS LIST

- **ASA –** acetylsalicylic acid
- **ACC –** American College of Cardiology
- **ACCF –** American College of Cardiology Foundation
- **AHA –** American Heart Association
- **ARC –** Academic Research Consortium
- **ARR –** Absolute Risk Reduction
- **CVA –** Cerebrovascular Accident
- **BCRI –** Brazilian Clinical Research Institute
- **IRB –** Institutional Review Board
- **CK-MB –** creatine phosphokinase-MB fraction
- **CRF –** Case Report Form
- **IUD –** Intrauterine Device
- **DSMB –** Data and Safety Monitoring Board
- **SAE –** Serious Adverse Event
- **RCT –** Randomized Clinical Trial
- **ESC –** European Society of Cardiology
- **Hgb –** Hemoglobin
- **Hct –** Hematocrit
- **HCor –** Heart Hospital (*Hospital do Coração*)
- **HR –** Hazard ratio
- **CPI –** percutaneous coronary intervention
- **RI –** Research Institute;
- **MI –** myocardial infarction
- **PI –** Principal Investigator
- **ITT –** Intention to Treat Principle
- **NSL –** normal superior limit
- **RSL–** reference superior limit
- **NNT –** necessary number to treat
- **MRI –** Magnetic Resonance Imaging
- **RR –** Relative risk

- **RRR –** Relative Risk Reduction
- **SCAI –** Society for Cardiovascular Angiography and Intervention
- **SUS –** Brazilian Unified Health System (*Sistema Único de Saúde*)
- **SUSAR –** Suspected Unexpected Serious Adverse Reaction
- **CT –** Computerized Tomography
- **ICF –** Informed Consent Form
- **UNL –** Upper normal limit
- **URL** – Upper reference limit
- **PO –** Oral route
- **WHF –** World Heart Foundation

1 INTRODUCTION AND RATIONALE

1.1 Percutaneous Coronary Intervention and the Acute Coronary Syndromes

The World Health Organization (WHO) has provided consistent estimates of deaths' causes by sex, age, for different countries and regions, based on systematic reviews of observational evidences. The most recent data show that cardiovascular diseases (CVD), particularly the acute myocardial infarction (AMI), represent the main cause of death and disability in both sexes, both in Brazil and worldwide. Its increase is accelerated in developing countries, currently representing one of the most relevant public health issues.[1,2] Regarding the economic aspects, in 2009, direct and indirect costs for cardiovascular diseases in the American territory were estimated at approximately 475.5 billion dollars.[3,4] These values, in a brief association with the Brazilian reality, are higher than the annual Brazilian gross domestic product (GDP), which certainly increase the concern for developing countries, where the incidence and prevalence of acute myocardial infarction are growing. According to DATASUS data, in Brazil, between 1995 and 2005, a total of 362998 hospitalizations in SUS hospitals were caused by acute myocardial infarction with a 61% increase in the number of hospitalizations during the period.[1]

According to forecasts from the Global Burden of Diseases study, by Murray and Lopez[4], by the year 2020, there are indications that CVD will not only remain as the main cause of death, but it will also represent the main disability cause. Once the acute myocardial infarction represents one of the main public health issues in Brazil and in the World, the search for interventions with proven benefits in reducing the incidence of this disease and its complications becomes a priority for physicians, patients, and health system managers.

Acute coronary syndromes include conditions such as myocardial infarction and unstable angina and are caused by atheroma plaques ruptures and with coronary bed occlusion, either total or partial. There are several therapeutic measures known to be beneficial for patients with acute coronary syndrome, including percutaneous coronary intervention that aims to open the occluded coronary bed.[5]

After performing a percutaneous coronary intervention (PCI) with stents implantation, it is observed a variable incidence (5 to 20% of the procedures) of post-procedural myocardial infarction (MI). This outcome is defined by the international taskforce (ESC/ACC/AHA/WHF) as the elevation within 48 hours after the procedure of troponin or creatine phosphokinase fraction MB

(CK-MB) levels >3 times the upper normal limit for patients with normal pre-procedural levels, or as a 20% increase in relation to the value before angioplasty for those with altered markers of myocardial necrosis at baseline.[6] The variable incidence is most likely related to the current clinical syndrome and to the anatomical complexity of the patient. In most cases, peri-procedural MI may occur without the manifestation of angina symptoms or definitive electrocardiographic changes.

The relevance of measuring this outcome lies on the fact that observational studies have suggested an independent association of this event with total and cardiovascular mortality. In this sense, *Stone e col.* have shown a progressive decrease in late survival, in an ascending geometric relation, after the evidence of this marker elevations >5 times, >8 times, and even >10 times the upper normal limit.[7] Consistently with these findings, on the *Tardiff e col.* study, it was observed an association between CK-MB increasing after revascularization by PCI or cardiac surgery and the risk of major cardiovascular events.[8]

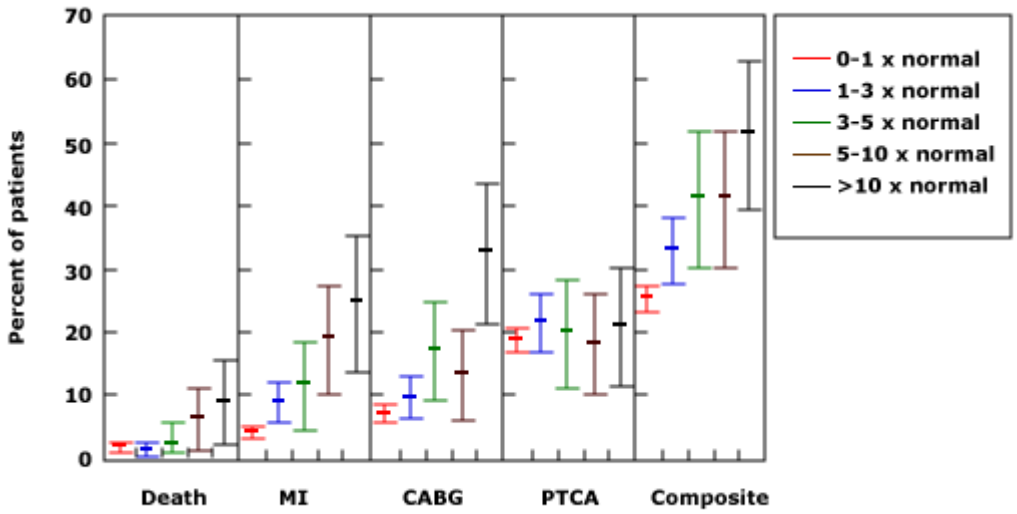


Figure 1. CK-MB and major cardiovascular events association

Source: Tardiff BE, Califf RM, Tcheng JE et al. J Am Coll Cardiol 1999; 33(1):88-96.

The Italian study recently published by *Cavallini e col.* had similar findings, suggesting an independent association between post-procedural CK-MB increasing and long-term total mortality.[9]

The physiopathogenesis of periprocedural MI is most likely related to the extent of endothelial damage caused by the procedure, what propitiates the occurrence of complications, both mechanical, such as occlusion of secondary branches and distal dissection of the target vessel, and embolic, such as displacement of thrombi into the distal circulation or of residues of fragmented atheroma after the several target vessel dilatation phases. These residues of microscopic clusters composed by cholesterol crystals, fibrin, platelets, inflammatory cells, endothelin and angiotensin II cause damage, at variable degrees, to the coronary microcirculation.[10] It is still added to this scenario the vasoactive substances released by stimulation during the stent implantation. These phenomena, embolics, have been referred to as "slow flow" or "no reflow", depending on the level of damage, with loss of the anterograde coronary flow normality and consequently of tissue perfusion.

The atherosclerosis involves in its pathogenesis inflammatory mechanisms causing endothelial injury and predisposing to plaque instability and its consequent rupture. The search for strategies that make these plaques more stable has been the subject of extensive clinical research and the role of statin has had important relevance in plaque control due to its pleiotropic effects.

1.2 Pleiotropic Effects of Statins

Statins are particularly known for their action in reducing cholesterol, however, their benefic effects go beyond this reduction. The myocardial protection takes place by inhibiting the 3-hydroxy-3methylglutaryl coenzyme A reductase, blocking the formation of mevalonate (precursor of cholesterol) and promoting the so-called pleiotropic effects.[11,12] Such effects direct benefits the endothelial function through the regulation of nitric oxide synthesis, stabilizing vulnerable plaques, due to the decrease of metalloproteinases activity. In addition, they reduce the intercellular adhesion molecules and decrease the circulating pro-inflammatory biochemical markers, e.g. C protein.[13]

Therefore, its administration by a loading dose, through oral route, before the PCI with stent implantation, may provide attenuation of the inflammatory cascade, acting on the reactivity reduction and increasing the target stenosis stability, benefit that extends to other stenoses with vulnerability potential and consequent rupture, stabilizing the clinical scenario and, potentially, reducing the cardiovascular events in both short and long terms.

1.3 Evidences from Randomized Clinical Trials and Systematic Reviews for pre-procedural Statins Usage

The first randomized clinical trial addressing this question was published in 2004 (ARMYDA – Atorvastatin for Reduction of Myocardial Damage During Angioplasty). In this study, the authors recruited 153 patients who had not previously used a statin and that underwent PCI with stent implantation for the treatment of stable coronary disease. Patients were randomized to receive atorvastatin 40mg or placebo 7 days before the procedure. By the end of 30-day analysis, those who were pre-treated with the drug presented a significant reduction (5% vs. 18%; p=0.025) in the composite outcome (death, MI and new target vessel revascularization).[14]

Subsequently, the same authors developed the ARMYDA-ACS clinical trial, in order to evaluate of these results in the context of acute coronary syndrome. At randomization, patients were allocated into two groups, either to receive placebo or statin, on the therapeutic approach of atorvastatin 80mg 12 hours associated to an additional dose of 40mg 2 hours before PCI. Again, benefits were observed in reducing the same composite outcome (5% vs. 17%; p=0.01). The incidence of MI after the procedure was of 5% vs. 15% (p=0.04) for the active treatment vs. placebo, respectively.[15]

On the NAPLES II trial (*Novel approaches for preventing or limiting events (Naples) II Trial*) the researchers showed that statins-naïve patients who received 80mg of atorvastatin prior to PCI with stent implantation presented a lower incidence of post-procedural MI rates (9.5% vs. 15.8%; p=0.0140).[16] Once these evidences were established, the authors tried to verify the potential benefit of administering a higher loading dose of statins by comparing previous users of this drug class vs. nonusers. Among statin users from the ARMYDA-RECAPTURE trial, a 80-mg dose of atorvastatin 12 hours before planned PCI followed by a reload of 40mg 2 hours after PCI, has also reduced the occurrence of this complication, measured by the sum of the occurrence of adverse events at 30 days (9.4% vs. 3.7%; p=0.037), when compared to patients in placebo group. It is important to emphasize that, in this trial, that the benefit of atorvastatin reload was more evident in patients who underwent the interventionist procedure during an acute coronary syndrome without ST segment elevation (Figure 2).[17]

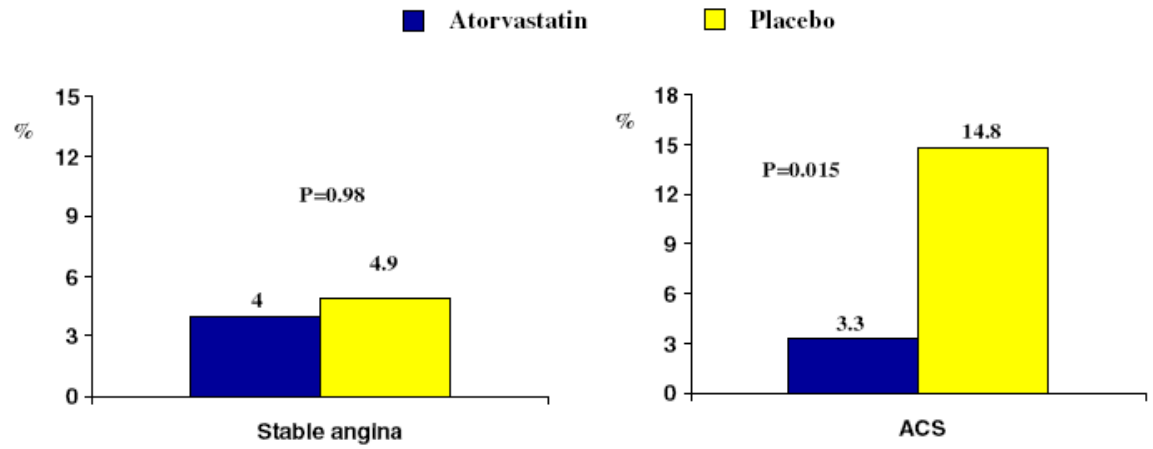
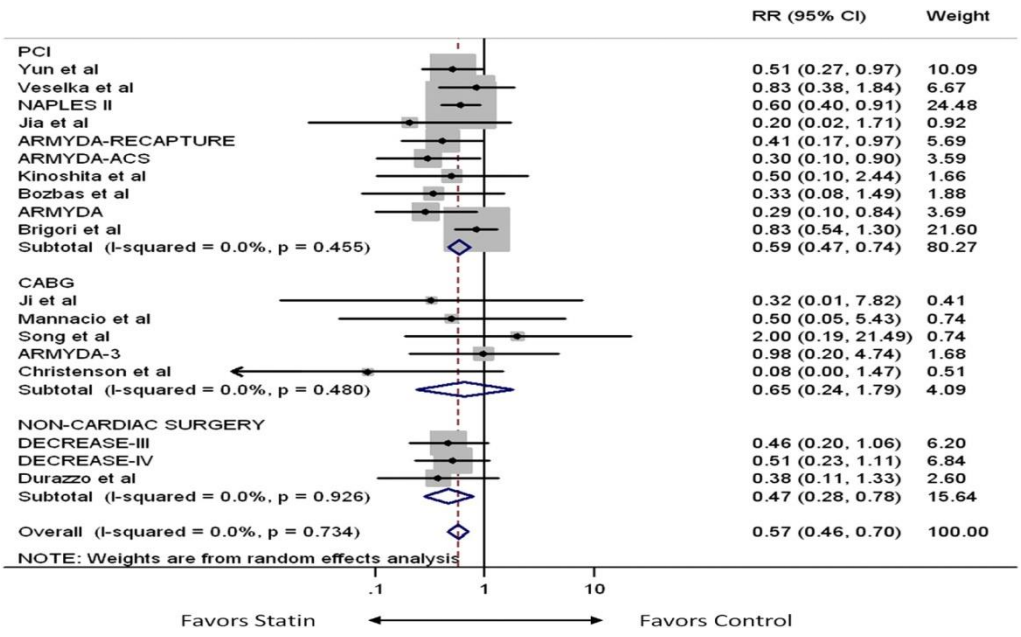


Figure 2. ARMYDA-RECAPTURE Trial about the benefit of pre-procedural statin in reducing adverse events in patients with stable disease vs. acute coronary syndrome

Source: Di, Patti, Pasceri, Gaspardone et al. ARMYDA-RECAPTURE. J Am Coll Cardiol, 2009; 54(6):558-565. [17]

There is little evidence about this on those patients having myocardial infarction with ST segment elevation. The STATIN STEMI Trial conducted by Kim and col., assessed 171 statin-naive patients having acute coronary syndrome with ST segment elevation, in which a loading dose (atorvastatin 80mg) offered at the emergency room showed not being able to reduce major cardiovascular events after 30 days when compared with patients that received a lower dose of the same drug (10mg). However, an improvement in the coronary flow was observed after angioplasty in those who had received the higher dose of atorvastatin.[18]

A recent systematic review with meta-analysis has included 21 randomized clinical trials, 4805 patients. Of these, 10 clinical trials were performed with patients that underwent PCI (including the studies previously discussed). That meta-analysis of these studies suggested a reduced risk of periprocedural MI [RR = 0.59 (95%CI): 0.47-0.74]. It was observed a non-significant reduction in total mortality with statins usage, as shown in the figures below.[19]



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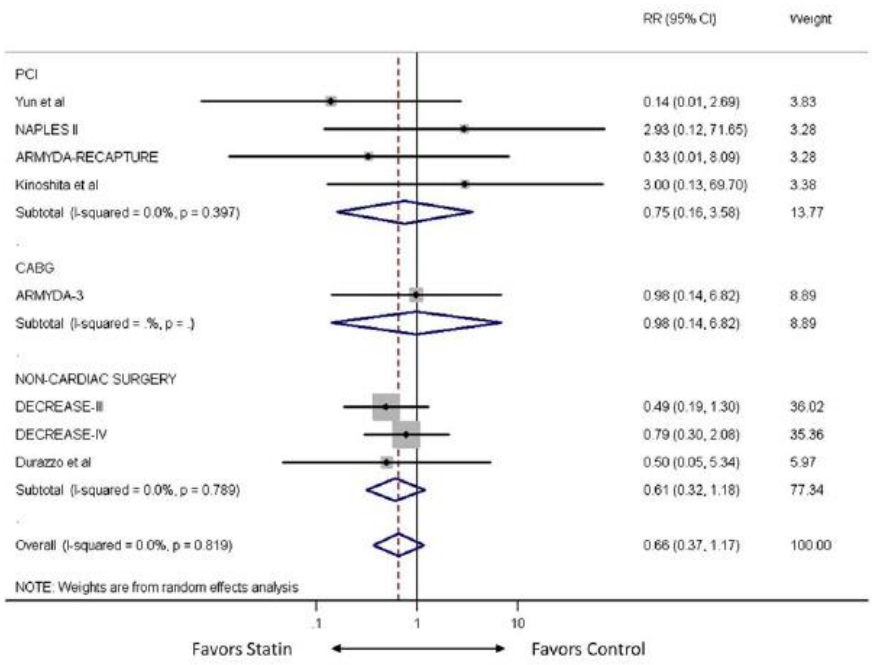
291 Figure 3. Meta-analysis about the pre-procedural statin usage on the post-procedural infarction reduction

292 Source: Winchester, Wen, Xie, Bavry. J Am Coll Cardiol, 2010; 56(14):1099-1109.



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294 Figure 4. Meta-analysis about the pre-procedural statin usage and mortality

295 Source: Winchester, Wen, Xie, Bavry. J Am Coll Cardiol, 2010; 56(14):1099-1109.

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Despite that most studies so far have used atorvastatin to test their interventions, recently, the the ROMA study data (ROsuvastatin Pretreatment in Patients Undergoing Elective PCI to Reduce the Incidence of MyocArdial Periprocedural Necrosis) was presented at the Transcatheter Cardiovascular Therapeutics (TCT). In was shown that a single dose of rosuvastatin 40mg, administered 24 hours before elective stent implantation, was able to reduce the incidence of death, infarction or stroke after 6 months, in addition to decrease the incidence of periprocedural infarction.[20]

1.4 Rationale for Using of a "Loading Dose" of Statin in Higher doses some hours before PCI

The meta-regression published by Winchester and col. suggests that there is no relationship between timing of statin administration and the effect, i.e., there were benefits in both those who received statin 7 days or 12 hours before the procedure.[19]

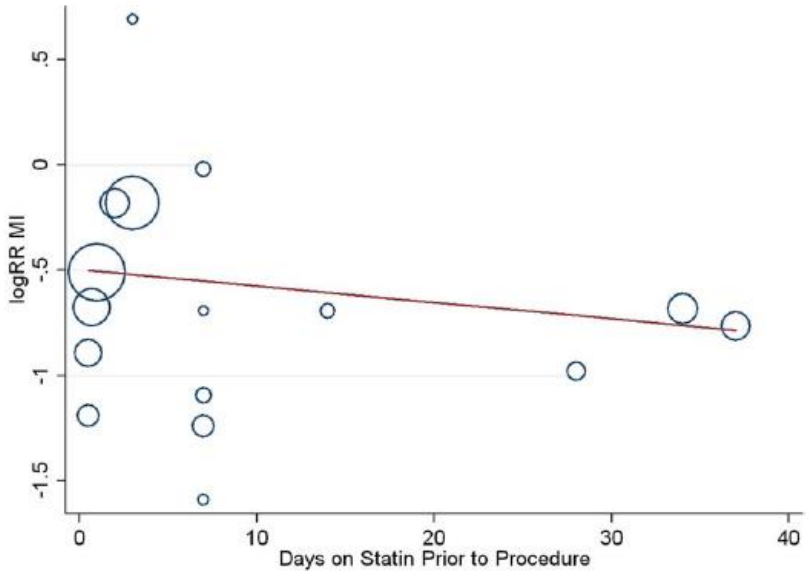

Figure 5. Meta-regression – timing of statin treatment before PCI and clinical events

Source: Winchester, Wen, Xie, Bavry. J Am Coll Cardiol, 2010; 56(14):1099-1109.

To the best of our knowledge, there are no studies so far that have shown benefit in statins usage few hours before the procedure (3-6 hours). However, based on the pleiotropic effects of statins, as well as on the results suggested by the meta-regression analysis, there is a sound rationale to test this hypothesis and only one large randomized clinical trial will be able to answer this question.

1.5 Why is a New Randomized Trial Needed?

Several reasons make a randomized clinical trial with sound methodology and adequate statistical power necessary, namely:

- The recent percutaneous coronary intervention ACC/AHA/SCAI guidelines recommend pre-procedural statin usage (IIa Grade, A/B evidence level), but this recommendation is not definitive and there are still doubts about the definition of adequate temporality for its administration and about the ideal dose.[21] Thus, a large randomized clinical trial will be able to provide robust information that could even influence those guidelines.
- In addition, although most patients with Acute Coronary Syndrome are underwent to the invasive study, not all of them are underwent to percutaneous coronary intervention, since some of these patients may benefit from other therapeutic strategies, such as myocardial revascularization surgery. Thus, it is not possible to predict which patients will not undergo percutaneous coronary intervention prior to angiocoronariography. For this reason, one previously unanswered question and that will be assessed by the SECURE-PCI Trial is whether a high dose of statins (atorvastatin 80mg before the procedure followed by a reload of 80mg after 24 hours) is able to reduce major cardiovascular events up to 30 days in patients with ACS with planned percutaneous coronary intervention. Only one study involved 383 patients and included previous statin users. Since this may be the current reality, and therefore represents one considerable part of eligible patients to SECURE-PCI Trial. Thus, it becomes necessary to perform a study with adequate sample size to define this issue.
- There is a need to identify potential subgroup effects (e.g. patients with ST segment elevation AMI, especially those on prior statins therapy).

- Previous studies have suggested benefits from statins before PCI on the peri-procedural infarction outcome with no clear demonstration of this benefit on total mortality and other clinically relevant outcomes. In this sense, 10 randomized clinical trials were conducted so far, involving less than 3000 patients and only one of them has included chronic statin users. In order to robustly assess the effect of statins in PCI on major cardiovascular events in 30 days, it would be necessary to include approximately 4192 patients. In order to obtain enough evidence to answer this issue in a conclusive and definitive manner, the conduction of a new clinical trial larger than the ones so far conducted should be considered.
- The majority of patients included in previous small trials are those with stable coronary artery disease, and more studies are needed in those with acute coronary syndrome.

1.6. Philosophy of large and simple pragmatic clinical trials

Large and pragmatic Randomized Clinical Trials (RCTs) can provide reliable evidence of the risk-benefit ratio of widely used treatments with moderate effects (relative risk reduction between 10 and 30%) on patient-relevant outcomes. In order to make reliable decisions in a large number of patients, we have to be sure about the therapy effects on death from any cause (and other relevant outcomes) in different patient groups. In general, a quality evidence on the use of a given therapy to whom should receive it can only be generated by large-scale RCTs with thousands of patients' recruitment. These studies are only feasible and financeable if they are simple. The moderate effects of the treatment are the most plausible ones and can be of great value if they are easy and have wide application. The reliable assessment of such moderate effects depends, however, on the randomization of an expressive number of individuals, sometimes hundreds, if not thousands, of patients.

The treatment of myocardial infarction provides a good example of successful studies of this type. The ISIS, GISSI, and COMMIT trials quickly randomized thousands of patients with MI worldwide by addressing important issues, with simple protocols, based on the uncertainty eligibility of both physicians and patients regarding what is the best treatment, and for requiring a minimal extra workload from participants. With this simple and direct design, physicians with uncertainties about the best approach to treat their patients end up considering randomizing patients in trials as easy as to arbitrarily treat them outside this RCTs. Besides that, these large-scale RCTs have

produced clear results with substantial impact on clinical practice. As result from these and other large trials, thousands of unnecessary deaths are being avoided annually.

The SECURE-PCI trial intends to randomize a large number of patients with acute coronary syndrome with planned PCI. To make this recruitment feasible, the procedures of the SECURE-PCI trial are simple and direct, planned not to impose any additional workload for participating physicians besides the one involved in patients' treatment. Print and online reports will keep investigators informed about the study progress.

2 OBJECTIVES

2.1 Primary objectives

To determine whether the administration of a loading dose of atorvastatin 80mg before the percutaneous coronary intervention combined with a booster dose of 80mg 24 hours after the procedure, is able to reduce the major cardiovascular events rate (MACE – major cardiovascular events), defined as a composite outcome of mortality, non-fatal MI, non-fatal stroke or unplanned coronary revascularization in 30 days, in patients with acute coronary syndrome with planned percutaneous coronary intervention.

2.2 Secondary objectives

To assess the effect of a loading dose of atorvastatin before coronary angioplasty followed by a booster dose 24 hours after the intervention on composite cardiovascular outcome (already described) in 6 months and 12 months and on individual components in 30 days, 6 moths and 12 months. Besides, it aims to assess the occurrence of the following clinical outcomes:

- Bleeding at discharge or day 7
- Cardiovascular mortality at 30 days, 6 months and 12 months
- Stent thrombosis at 30 days, 6 months and 12 months
- New target vessel revascularization at 30 days, 6 months and 12 months
- Coronary revascularization

It will be analyzed the rates of adverse events, such as hepatotoxicity (through the collection of liver transaminases – GOT and GPT) and myopathy (collection of creatine phosphokinase – CPK) at 30 days.

3 METHODS

3.1 Study Design

Randomized clinical trial with concealed allocation, multicenter, national, pragmatic, blinded outcome assessment and with intention-to-treat analysis. The recruitment will be competitive at several centers in Brazil, aiming to recruit 4192 patients.

3.2 Eligibility

3.2.1 Inclusion Criteria

Patients of both genders, older than 18 years that had accepted to participate in the study by signing the Informed Consent Form, and during the acute coronary syndrome with intention to be treated with angioplasty on the same hospitalization in up to 07 (seven) days from ACS diagnosis (including those with ST segment elevation with planned primary angioplasty) that present at least 2 of the following criteria[22,23]:

- ✓ Angina-like chest pain or ischemic equivalent;
- ✓ Electrocardiographic abnormalities (ST segment elevation higher than 2mm on precordial leads and 1mm on peripheral or new left bundle branch block, ST segment depression of at least 0.5mm or T wave inversion greater than 0.2mV) on at least two contiguous leads;
- ✓ Abnormalities above the upper normal limit for myocardial necrosis markers (troponin and/or CKMB).

Previous use of statins (for any time prior to inclusion in this study) is not considered an exclusion criteria for the SECURE-PCI Trial. In this way, both “statin-naive” patients and patients that were previously exposed to this drug class will be included. However, the patient could not have received maximum statin dose in the last 24 hours prior to PCI to be eligible due to safety concerns. It is considered maximum dose as follows: Atorvastatin 80mg; Rosuvastatin 40mg; Sinvastatin 80mg; Pravastatin 40mg or Fluvastatin 80mg. Potential differences in the treatment effect among these patients will be assessed using pre-specified subgroup analysis.

3.2.2 Exclusion Criteria

- Pregnant or breastfeeding women and women under 45 years old not using effective contraceptive methods (regular use of contraceptive pills, IUD, tubal ligation).
- Previous inclusion in this study.
- Refusal to provide the Informed Consent Form (ICF).
- Concurrent participation in other randomized clinical trials with any lipid-lowering drugs .
- Drug hypersensitivity.
- History of advanced liver disease (primary biliary cirrhosis, sclerosing cholangitis, acute hepatitis, persistent elevations of liver transaminases >3 times above the upper normal limit).
- Use of any statin at maximum dose (see above) in the last 24 hours before PCI.
- Fibrate intake in the last 24 hours prior to using the study loading dose.

3.2.3 Patient Withdrawal

It will only occur if patient withdraws consent. In case patient decides not to follow the study procedures, but maintains the consent for using the clinical information, his/her data will be used.

3.3 Randomization Method and Maintenance of Allocation List Confidentiality

The randomization list will be generated using a validated software (available at the Clinical Trials System, of RI HCor) by blocks of variable sizes and it will be stratified by center and by kind of Acute Coronary Syndrome (with or without ST segment elevation), and it will be considered ACS with ST elevation only the cases with planned primary PCI. In order to include the patient in the trial, the investigator will have to access the SECURE-PCI Trial website and fill in a simple case report form in order to generate that patient randomization. The randomization by the Clinical Trials System of RI HCor (https://servicos.hcor.com.br/iep/estudoclinico) is characterized as a central randomization that ensures the randomization list confidentiality. In other words, the investigators responsible for patients' inclusion in the study will not be able to know which group each patient will be allocated to.

3.4 Study Interventions

3.4.1 Study Procedure

After providing the ICF, patient will be randomized at a 1:1 ratio to receive a dose of atorvastatin 80mg (or matching placebo) before PCI. For patients with Acute Coronary Syndrome without ST

elevation, this loading dose should be administered within 2 to 12 hours before the procedure. For patients with Acute Coronary Syndrome with ST elevation, the loading dose should be administered as soon as possible. According to protocol, patient will receive the booster dose of 80mg 24 hours after the procedure. Patient allocated to the control group will receive the matching placebo. Randomization will be performed through an electronic system, whose register is previously done and patient will receive an individual identification, therefore, the electronic randomization gives a number of a numbered treatment kit that is already available at the institution, whose content can be either atorvastatin or placebo).

For all study patients (both experimental and control groups) it will be instructed to use atorvastatin 40mg after the procedure, starting on the day after the day the booster dose was given until the 30-day follow up visit, and after this period, statin usage will be recommended, but the choice of which agent and dose will be at the medical staff discretion.

3.4.2 Patient Recruitment

Patients will be recruited at Emergency Rooms and Interventional Cardiology Centers. About 75 sites in Brazilian will be selected to participate in the trial. Recruitment will be competitive, until the total number of study patients is reached (n = 4192).

3.4.3 Invited Sites

Approximately 75 sites will be invited to participate in the study, with the help of the ACT, ACCEPT, members of SBHCI network and collaborative sites from BCRI.

3.4.4 Laboratory Exams Protocol

Serum measurements will be performed in all patients included in this trial, according to the time points described below. CKMB and/or Troponin measurement will be performed in all patients included in the trial, prior to procedure (hours before or immediately after) and at two sequential intervals after the procedure from 6 to 12 hours and from 18 to 24 hours. Serum measurement of other exams (including lipid profile) may be done after the first fasting period, i.e., on the morning after admission. Patient discharge will be determined by the medical staff. AST (aspartate aminotransferase), ALT (alanine aminotransferase) and CPK (creatine phosphokinase) measurements will be done at the planned visit 30 days after procedure, in order to evaluate the safety of the drug under investigation. The list below summarizes the study procedures.

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Initiation Visit
ICF Signature
Serum measurement of CKMB and/or troponin at pre-angioplasty
Glutamic-pyruvic transaminase (GPT/ALT),
Glutamic-oxaloacetic transaminase (GOT/AST)
Creatine phosphokinase (CPK)
Lipid profile (1 hour before, immediately after PCI or on the first fasting period of hospitalization)
Electronic randomization
Study drug loading dose administration [atorvastatin 80mg or matching placebo (1 tablet)]
Procedure performance (Catheterism / angioplasty)
Study drug booster dose administration [atorvastatin 80mg or matching placebo (1 tablet) 24 hours after procedure]
Electronic form completion
CKMB and/or troponin measurements 6 – 12 hours after angioplasty
CKMB and/or troponin measurements 18 – 24 h hours after angioplasty
Maintainance drug – atorvastatin 40 mg daily, for both groups, it should start on the day after the day of booster dose until the 30-day follow up visit.
30-day Visit
Clinic visit (in person)
Serum measurement of lipid profile, transaminases (AST and ALT) and CPK
Electronic forms completion
6-month Follow up
Phone contact
Electronic forms completion

1-year Follow up
Phone contact Electronic forms completion

3.5 Study co-interventions

3.5.1 Drugs

By using the concealed randomization of an adequate number of patients, both groups will be balanced in terms of known and unknown factors that could potentially influence the outcomes, including pharmacological co-interventions and characteristics of the procedure (PCI).

Due to its pragmatic design, the co-interventions choice will be at the medical staff discretion. Nevertheless, the use of the following agents listed below will be strongly recommended to all sites (except if contraindications are present).

Drug	Dose	Contraindication
ASA	Loading dose: 160-325mg and Maintenance of 100mg/day	History of allergy or active gastrointestinal (GI) bleeding.
Clopidogrel	Loading dose: 300-600mg Maintenance of 75mg/day	Active GI bleeding.
Glycoprotein IIb/IIIa inhibitors	Abciximab (0.25µg/Kg bolus + Maintenance of 0.125µg/Kg in 12 hours)	Active internal bleeding; GI or genitourinary bleeding; history of stroke in less than 2 years; bleeding diathesis; thrombocytopenia (< 100.000).
Unfractionated heparin	Loading dose: 60U/kg (4000U max.) Maintenance: 12U/kg/h (1000U/h max.)	Bleeding diathesis; GI bleeding; brain hemorrhage; severe coagulopathies; liver failure; known hypersensitivity to heparin.
Low-molecular-weight heparin	< 75 years: 1mg/kg SC 12/12h > 75 years: 0.75mg/kg 12/12h Renal adjustment: 1mg/kg/day	Bleeding diathesis; brain hemorrhage; severe coagulopathies; liver failure; known hypersensitivity to heparin.
Fondaparinux:	2.5mg subcutaneous once a day.	Active bleeding; known hypersensitivity to fondaparinux or to any of the excipients; severe renal failure (creat cl < 30

		ml/min).
ACE inhibitors	Captopril 12.5mg 12/12h; enalapril 2.5mg 12/12h; ramipril 2.5mg 12/12h.	Bilateral renal artery stenosis; pregnancy; history of angioedema due to ACE inhibitors.
β-blockers	Initial PO dose: propanolol 20mg 8/8h; metoprolol 25mg 12/12h, atenolol 25mg daily; carvedilol 3.125g 12/12h. IV dose: metoprolol 5mg	Cardiogenic shock or signs of a low cardiac output; second or third degree atrioventricular block; active asthma; reactive airway disease.

Source: Nicolau JC et al. Arq Bras Cardiol 2007; 89(4) e89-e131[22]; Piegas S et al. Arq Bras Cardiol. 2009;93(6 supl2): e179-e264[23].

3.5.2 Planned Percutaneous Coronary Intervention

The percutaneous coronary intervention will be performed according to the current clinical practice of the Institution, using either the transfemoral or the transradial access. Stents implantation, as well as stent characteristics, will be at the interventional cardiologist discretion. After the procedure, patients will be forwarded to the adequate hospitalization unit, except for the occurrence of major intercurrences.

Those patients who were randomized and have not undergone angioplasty will be analyzed by the intention to treat principle. For these patients the steps that should be taken are described in appendix 1.

3.6 Blinding

The two tablets (atorvastatin and matching placebo) used as loading dose in the study will be visually similar in terms of size, shape and color. Thus, in the SECURE trial, patients, investigators, outcome assessors and the statistician in charge of data analysis will be blinded for treatments identity throughout the study period.

3.7 Outcomes

All outcomes will be assessed by an Independent and Blinded Adjudication Committee (Validation). This Committee will be composed by physicians with expertise in multicenter clinical trials conduction in this field. All events will be revised by at least 2 independent members of this Committee.

3.7.1 Primary Outcome

The primary outcome of SECURE-PCI Trial will be major cardiovascular events (MACE - major cardiovascular events), defined as a composite outcome of total mortality, myocardial infarction, nonfatal stroke or unplanned coronary revascularization in 30 days.

3.7.1.1 Death

3.7.1.1.1 Death Classification

Deaths will be classified as Cardiovascular, Non-cardiovascular, or Unknown. The cause of the death is determined by the main condition that caused the death, not the immediate modality of the death. All death causes will be considered of cardiovascular nature, unless there is one non-cardiovascular cause clearly defined, except for the death without any additional information that will be classified as Unknown cause. Cardiovascular death includes, but is not limited to, atherosclerotic coronary heart disease (acute myocardial infarction, sudden cardiac death, non-sudden death associated with cardiac symptoms with gradual worsening, unwitnessed death without defined alternative cause, death related to the cardiac surgical procedure or to coronary angiography), vascular atherosclerotic disease (cerebrovascular disease including ischemic and hemorrhagic cerebrovascular stroke, aortic, mesenteric, renal vascular, or peripheral arterial disease, death related to the non-coronary vascular procedure), and other cardiovascular (pulmonary embolism, endocarditis, congestive heart failure, cardiac valvular disease, arrhythmias). Example of non-cardiovascular death includes the primary cause of death as being infectious, related to malignancy, pulmonary, gastrointestinal, accidental suicide, renal.

Cardiovascular death will be then classified as sudden, non-sudden and unwitnessed.

3.7.1.1.1.1 Cardiovascular Sudden Death

Sudden cardiovascular death is defined as unexpected that is:

a) witnessed: occurring within 60 minutes of the symptoms onset, in the absence of another clearly non-cardiovascular cause. **OR**

b) unwitnessed: within 24 hours of being seen alive, in the absence of pre-existing conditions of circulatory failure or other non-cardiovascular cause of death.

All sudden deaths will be classified according to the fulfillment of criteria (a) or (b).

3.7.1.1.1.2 Non-cardiovascular Sudden Death

This category refers to patients with symptoms from cardiovascular nature and that have had gradual deterioration prior to death. It includes all patients with cardiovascular death who did not meet the criteria of cardiac sudden death or unwitnessed cardiovascular death.

3.7.1.1.1.3 Unwitnessed cardiovascular death

Death of unexpected occurrence, without the patient having been seen in the last 24 hours and having no other major causes of death identified.

3.7.1.2 Myocardial Infarction

All AMI events will be classified/defined within three general categories, according to the adjudication committee, using the following definitions as guidelines:

3.7.1.2.1 Periprocedural Myocardial Infarction

Periprocedural Myocardial Infarction is defined as any one of the following criteria. Cardiac ischemic symptoms are not necessary.

1. If normal cardiac biomarkers at admission:

   - CKMB elevation ≥3 times the upper normal limit (UNL) or Troponin ≥5 times the upper reference limit (URL) (if CKMB is not available) within 48 hours after PCI

OR

2. If elevated cardiac biomarkers at admission and tending to decrease before the AMI suspicion:

   - CKMB elevation ≥3 times the UNL or Troponin ≥5 times the URL (if CKMB is not available) **AND**

   - Biomarkers elevation greater than or equal to 20% when compared to pre-procedural value (baseline or 2 hours sample)

OR

3. If elevated cardiac biomarkers at admission and tending to increase or are unknown before the AMI suspicion:

- New ischemic symptoms for at least 20 minutes **AND**
  - Additional elevation of CK-MB or Troponin levels at post-procedural, with levels of at least CK-MB ≥3 times the UNL or Troponin ≥5 times URL (if CK-MB is not available) **AND** at least one of the following:
    A) Report of complication during the percutaneous coronary intervention, registered at cineangiocoronarygraphy **OR**
    B) New ischemic changes in the 12-lead ECG during or after the procedure

OR

4. Evidence of AMI on the autopsy (if not index AMI)

Summary of definitions of periprocedural AMI

Cardiac biomarkers at admission	Angiographic evidence; ECG; ischemic symptoms	CKMB
Normal baseline (normal markers within 1 to 2 hours post-procedural will be considered "normal baseline")	Not necessary	CKMB ≥3 times the UNL or Troponin ≥5 times the URL (if CKMB is not available)
Elevated tending to decrease without any ischemic manifestation since the elevation moment to angioplasty	Not necessary	New elevation of CKMB ≥3 times the UNL and/or Troponin ≥5 times the URL (if CKMB is not available) and a 20% increase in relation to the smallest pre-procedural value
Abnormal baseline and tending to increase at post-procedural or unknown at the admission moment	New ischemic symptoms for at least 20 minutes and report of angiographic complications during PCI or new ischemic changes in the 12-lead ECG	Continuous elevation of CKMB ≥3 times the UNL and/or Troponin ≥5 times the URL (if CKMB is not available)

3.7.1.2.2 Spontaneous Myocardial Infarction (after 48 hours from PCI)

Spontaneous acute myocardial infarction is defined by elevation and/or decrease of cardiac biomarkers (CKMB or troponin) with at least one value above the reference and at least one of the following criteria:

- Clinical presentation consistent with ischemia
- Electrocardiographic evidence of acute myocardial ischemia
- Development of new pathological Q wave
- Evidence on imaging test of new change in segmental contractility of myocardial wall or loss of viable myocardium

The autopsy exam with AMI evidence may be used as isolated criterion for the infarction.
If the biomarkers are elevated due to a previous infarction, the spontaneous AMI diagnosis will need the following:

- Evidence that cardiac biomarkers values are decreasing before the AMI suspicion **AND**
- CKMB ≥3 times the UNL or Troponin ≥5 times the URL and this value corresponds to a 20% increase of the biomarkers in relation to the smallest value after angioplasty.

  And at least one of the following:

  - Clinical presentation consistent with ischemia
  - Electrocardiographic evidence of acute myocardial ischemia
  - Development of new pathological Q wave
  - Evidence on imaging test of new change in segmental contractility of myocardial wall or loss of viable myocardium

Autopsy exam with evidence of new AMI may be used as isolated criterion for the spontaneous infarction.

3.7.1.2.3 Perioperative myocardial infarction (myocardial revascularization surgery)

Perioperative infarction related to myocardial revascularization surgery (CABG) is defined according to the following criteria. Myocardial ischemia symptoms are not necessary.

- Biomarkers elevation within 72 hours from CABG with CK-MB >5 times the UNL or Troponin >10 times the URL (if CK-MB is not available) **AND**

- No evidences that biomarkers are elevated before procedure

OR

- Evidence that cardiac biomarkers are decreasing before procedure **AND**
- ≥ 50% increase on cardiac biomarkers - **AND**
- One of the following:
    - New persistent pathological Q wave for 30 days
    - New persistent left bundle branch block not related to frequency
    - New graft or native coronary occlusion documented on angiography
    - Other complication during the operative event resulting in myocardial loss
    - Evidence on imaging test of new loss of viable myocardium

OR

    - Evidence of AMI on autopsy

3.7.1.3 Stroke

Stroke is defined as an acute focal neurological deficit of sudden onset:

a) that is not reversible in 24 hours or that results in death (in less than 24 hours) and is not due to an identifiable cause (e.g. tumor or trauma) **OR**

b) that resolves in <24 hours and is accompanied by a clear evidence of stroke in brain imaging test.

Stroke will be subclassified in 4 subtypes:

- Non-hemorrhagic cerebral infarction: it is the stroke without intracerebral blood focal collections in brain imaging test. This category will be subclassified between suspects of embolism versus other.
- Non-hemorrhagic cerebral infarction with hemorrhagic transformation: it is the blood cerebral infarction that seems to represent hemorrhagic transformation and not primary hemorrhage. Hemorrhagic conversion usually occurs at the cortical surface. Deeper hemorrhagic transformation requires evidence of non-hemorrhagic infarction at the same vascular territory. Evident micro-hemorrhages on magnetic resonance imaging (MRI) in both the cortex and the deeper cerebral structures are

not considered to be consistent with the hemorrhagic transformation outcome.

- Primary bleeding (hemorrhage)
  - Intracerebral hemorrhage: stroke with focal collections of intracerebral blood seen in brain imaging tests (computed tomography (CT) or MRI) or in postmortem exam, not representing hemorrhagic conversion. Primary hemorrhages cause hematomas that are usually easily distinguished by their subcortical location and round or elliptical shape. Micro hemorrhages incidentally found in brain imaging tests in the absence of symptomatology will not be considered a primary intracranial hemorrhagic outcome.
  - Subarachnoid hemorrhage: collection of high density fluid in the subarachnoid space in brain imaging tests or presence of blood in the subarachnoid space at autopsy.
  - Uncertain: any stroke without brain imaging test (CT or MRI) or documentation by autopsy or if tests are inconclusive.

Subdural hematoma will not be classified as stroke, but will be classified as bleeding outcome (intracranial hemorrhage). Micro intracerebral hemorrhages will be classified into separate categories for analysis. Micro hemorrhage is defined as rounded focus of less than 10mm that appears hypointense and that are different of other causes of signal loss or echo in the MRI sequences gradient (e.g. vascular flow emptying, leptomeningeous hemosiderosis and non-hemorrhagic subcortical mineralization).

Transient ischemic attack is defined as:

a. a focal neurological deficit lasting <24 hours and no identifiable non-vascular cause (e.g. cerebral tumor, trauma), **AND**

b. absence of new infarction in brain imaging test (if available).

3.7.1.4 Coronary revascularization

a) Unplanned coronary revascularization is defined as coronary revascularization that was not planned at the first angiocoronariography performed due to ACS index event (inclusion criteria). The indication of an unplanned revascularization should be related to new findings (e.g. ischemic symptoms) and include both surgical and percutaneous

revascularization cases, both during hospitalization and after hospital discharge from index event.

It also includes revascularization attempt even without success. Potential ischemic events that fit the AMI criterion will not be validated with urgency coronary revascularization.

3.7.2 Secondary Outcomes

- Individual components of the composite primary outcome (total mortality, non-fatal AMI, non-fatal stroke and coronary revascularization) at 30 days, 6 months and 12 months.
- Cardiovascular mortality at 30 days, 6 months and 12 months.
- Assessment of the composite outcome of total mortality, non-fatal myocardial infarction and coronary revascularization at 6 and 12 months.
- Target vessel revascularization at 30 days, 6 months and 12 months.
- Stroke at 30 days, 6 months and 12 months.
- Coronary revascularization.
- Stent thrombosis at 30 days, 6 months and 12 months.

The secondary outcomes definitions are described below.

3.7.2.1 Target vessel revascularization

Target vessel revascularization is defined as a new percutaneous or surgical procedure resulting from restenosis of the target lesion segment. All target lesion revascularization will be guided by symptoms or by objective evidence of ischemia in noninvasive tests.

3.7.2.2 Stent thrombosis

The TIMI group defines stent thrombosis with the following criteria to determine whether the event was angiographically/pathologically confirmed or clinically confirmed:

3.7.2.2.1 Stent thrombosis angiographically or pathologically confirmed

Ischemic chest discomfort or ischemic syndrome determining coronary angiography and

angiographic confirmation of thrombosis or presumed thrombotic occlusion of the stent segment.

OR

Phatological confirmation of acute stent thrombosis at autopsy.

3.7.2.2.2 Stent thrombosis clinically confirmed

Unexplained cardiovascular death defined as sudden or unwitnessed death without a clear cause of cardiovascular origin.

OR

Acute ischemic death (defined as death after presentation of ischemic cardiac event at the stent territory with death occurring before confirmation of coronary angiographic diagnosis).

OR

Myocardial infarction related to target vessel is defined as one of the MI signs/symptoms below:

- Pain of cardiac origin and ST elevation >20 minutes;
- New Q wave on the electrocardiogram;
- Ischemic discomfort lasting >10 minutes and biomarkers elevation (1 time UNL not associated to the procedure, 3 times UNL within 48 hours from PCI, 5 times UNL within 48 hours from MRI).

AND

Evidence of either electrocardiographyc, echocardiographic or nuclear medicine occurrence at the territory of the previously implanted stent without angiographic evidence of stent thrombosis.

AND

No pathological or angiographic evidence of another guilty injury.

Stent thrombosis is defined according to the Academic Research Consortium (ARC)[26] criteria and is divided into three categories: definitive stent thrombosis, probable stent thrombosis and possible stent thrombosis, the definitions are below.

a) Definitive stent thrombosis: the stent thrombosis will be defined by the angiographic or pathologic confirmation.

- The presence of thrombus originating from stent or at 5mm proximal or distal from the stent and the presence of at least one of the criteria within a 48-hour window (the angiographic documentation of stent occlusion in the absence of clinical signs or symptoms will not be considered as stent thrombosis {silent occlusion}):
    - Onset of ischemic symptoms at rest
    - New ECG changes suggesting acute ischemia
    - Typical curve of cardiac biomarkers that represent AMI
    - Non-occlusive thrombus: non-calcified intracoronary thrombus ((spherical, ovoid or irregular) defined as filling failure or contrast retention (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material inside lumen, or visible embolization of intraluminal materials distal to obstruction.
    - Occlusive thrombus: TIMI 0 or 1 intrastent or proximal to the stent to the most proximal adjacent branch or main branch (originates from the lateral branch)
- Evidence of recent thrombus inside the stent determined by autopsy or by biopsy of tissue removed by thrombectomy.

b) Probable stent thrombosis: considered when thrombosis occurs after angioplasty and in the following cases:

- Death without a known cause within 30 days
- Any infarct related to acute ischemia in the implanted stent territory, without angiographic confirmation of stent thrombosis and in the absence of any other obvious reason, independent of time.

b) Possible stent thrombosis: Considered when any death of unknown cause occurs after 30 days from angioplasty until the end of follow up.

3.7.2.3 Bleeding

Hemorrhagic complications will be classified according to the bleeding criteria of TIMI Group

(Thrombolysis In Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) and ISTH (International Society on Thrombosis and Haemostasis).

3.8 Report of Serious Adverse Events and Unexpected Adverse Drug Reactions

Given the short treatment period, with high dose and considering the extensive experience and safety with this regimen including management at post-ACS, the occurrence of serious adverse events due to the use of atorvastatin is expected to be rare. In 10 similar randomized clinical trials previously conducted, the incidence of these events was extremely low.

In the SECURE-PCI Trial, we will systematically monitor the occurrence of these serious adverse events using standard forms and standardized definitions of the expected events including those of primary outcome. Unexpected adverse drug reactions will be quickly collected.

Serious Adverse Events (SAE): any medical occurrence that affects the patient or the clinical investigation subject, even if it does not have a causal relationship with the procedure, and that results in death, persistent or significant disability/incapacity, requires inpatient hospitalization or prolongation of existing hospitalization, causes a congenital anomaly/birth defect, is life-threatening, or is considered relevant at the investigator discretion during the course of a clinical trial.

Suspected Unexpected Serious Adverse Reaction (SUSAR): adverse reaction whose nature or severity is not consistent with the applicable information about the product.

The principal investigator of each site should notify the event to the Institutional Review Board of their Institution, to the Coordinator Site and to the Study Sponsor, within one working day after becoming aware of the event.

The Coordinator Site will be in charge of reporting all SUSARs to all study participating sites, so that each center can forward a copy for their respective Ethics Committees.

4 DATA ENTRY SYSTEM

Data management will be performed using the Electronic Data Capture (EDC) System. Case report forms (CRFs) will be transcribed through Web-chart and sent to the coordinator site and incorporated in a validation database.

4.1 Data Collection Form

Study CRFs will be entirely completed and submitted through Internet or Web; they will be electronically signed, the access will require a personal non-transferable password. The printed CRF copy may remain with the principal investigator attached as source document and must be signed by the investigator/coordinator responsible for the data collection or other persons (co-investigators) adequately authorized by PI on the delegation of responsibilities document.

5 STUDY DRUG

5.1 Presentation

Atorvastatin 40 and 80mg – tablet.

Loading dose: 1 tablet (atorvastatin 80mg or matching placebo) within 2 to 12 hours before procedure for ACS without ST elevation and as soon as possible at the earliest for ACS with ST elevation.

Booster dose: 1 tablet (atorvastatin 80mg or matching placebo) 24 hours after procedure.

Maintenance dose: atorvastatin 40mg (1 tablet) for all patients, starting on the day after the day the loading dose was given.

5.2 Drug Control

The study drug must be stored in a safe place with restrict access to professionals involved in the study. Strict control of the date of receipt, administration of each kit and the amount of drug administered to each patient must be available at all participating sites. There must be drug accountability for all drug kits, even those deliberately or accidentally destroyed by the investigator or by the patient. The drug must be stored in a dry place, protected from direct sunlight, at room temperature.

5.3 Responsibility for the Study Drug

The study drug will be donated to the RI-HCor, which will produce the coded kits and send them to the participating sites, in order to guarantee study blinding. This drug cannot be used for other purposes except those pertinent to the SECURE trial. At the end of the study, according to the

coordinator site directions, the investigator will be instructed about the procedures related to the drug.

5.4 Study Registration

The study is registered at ClinicalTrials.gov under identifier code: NCT01448642.

6 STATISTICS

6.1 Sample Size Calculation

Considering a primary outcome (MACE – major cardiovascular events) rate of 12.3% at 30 days, a relative risk reduction (RRR) of 25%, for a power of 90% and a two-tailed alpha of 5%, it would be necessary to include in the study at least 4192 patients.

The initial plan is to include 75 sites in Brazil, with mean inclusion of 60 patients per center, with an average of 2-3 patients per month, during a two-year period. Recruitment will be competitive between sites.

6.2 Statistical Analysis

All analysis will follow the intention-to-treat principle; therefore, the number of events will be tabulated for both the experimental and the control groups. Time until the occurrence of primary outcome or of secondary outcomes in both groups will be presented using Kaplan-Meier survival curve. The treatment effect, measured by the hazard ratio (HR), will be obtained using Cox regression. RRR and the necessary number to treat (NNT) will also be calculated to avoid the occurrence of an outcome. For all effect parameters, 95% confidence intervals will be reported. All analysis will consider a two-tailed alpha of 5% and will be performed on the R software, version 3.3.3. (R Foundation for Statistical Computing).[27]

Subgroup analysis has a greater validity when established a priori and limited to a small number, being biologically plausible and consistent with previous evidences. Pre-specified subgroup analysis includes: men and women; > or < 65 years old; patients with acute coronary syndrome with and without ST segment elevation; patients with and without prior statin usage (> 30 days); and patients that received pharmacological stents vs. patients that received conventional stents.

7 CLINICAL RESEARCH ETHICAL ASPECTS AND GOOD CLINICAL PRACTICE (GCP)

The SECURE-PCI trial will be conducted in accordance with national and international regulations as described in the following documents:

- Helsinki Declaration.
- Brazilian Resolution CNS 466/12 and related documents from the Ministry of Health.
- ICH Harmonized Tripartite Guidelines for Good Clinical Practice - 1996.

7.1 Study Approval

Prior to study initiation, the investigator must send a copy of the research protocol, ICF, and other relevant and requested documents to their Institution IRB. A registered cover letter and the IRB approval must be forwarded to the Study Coordinator Site. Additionally, all possible protocol amendments must be approved by the IRB of each participating site.

7.2 Informed Consent Form (ICF)

It will be requested the patient signature on the ICF. If the patient is unable to provide consent, it will be requested to their legal representative. The consent request and the study-related information provided to the patient or their legal representative should be conducted by the physician or the study coordinator. Both the patient and the professional assigned will have to date and sign two copies of the ICF; one copy will be given to the patient and the other must be filed with other study documents. Subjects will be clearly informed that participation is voluntary, and that they can withdraw consent to participate at any time without any effects on quality and conduction of subsequent medical treatment. The ICF proposed by the study must be evaluated by each participating site, and in case any change is needed, it must be approved by the Coordinator Site prior to IRB submission.

7.3 Data Confidentiality

No patient identification data will be sent to Data Management or to Study Management teams. Electronic CRFs will identify patient and sites by numbers. Data obtained from medical chart must be kept confidential by sites, stored in locked cabinets and the guarantee to anonymity of all data in interim and definitive reports must be ensured.

7.4 Follow up Reports

The investigator must submit written reports of study status to their Institution IRB in a semiannually basis, as well as a final report by the end of the study.

8 STUDY COORDINATION

8.1 Coordinator Site

The SECURE-PCI Trial Coordinator Sites will be: HCor Research Institute (RI-HCor) and Brazilian Clinical Research Institute (BCRI). Both have wide experience in large trials. The technical quality of RI-HCor and BCRI teams will provide guidance and support to all participating sites to ensure research protocol adherence. Both RI-HCor and BCRI have the necessary education and level of knowledge in research methods and biostatistics, as well as are supported by awarded career scientists. The Duke University Clinical Research Institute will validate all study statistical analysis.

8.2 Steering Committee

Members of the SECURE-PCI Trial Steering Committee will be responsible for supervising the clinical trial conduction, including making the decisions to suspend or modify study procedures as necessary, dealing with the challenges involved in protocol implementation, revising and interpreting data, as well as preparing the final manuscript. These will be performed through meetings (in-person or phone calls) held at least every three months. All other SECURE-PCI Trial Committees will report directly to the Steering Committee.

8.3 Publication Committee

Four members of the Steering Committee will be selected to compose a Publication Committee that will be responsible for writing the final manuscript and submitting it for publication. This committee will also manage the database and will be responsible for evaluating proposals for publications based on SECURE-PCI Trial data.

8.4 Independent Outcome Adjudication Committee

The clinical outcome assessment committee is responsible for validation according to the following outcomes: type of death (Cardiovascular versus non-cardiovascular), myocardial

infarction, stroke, recurrent ischemia requiring revascularization, coronary stent thrombosis and bleeding.

All suspect events will be in this committee's database. There will be an administrative review of each outcome to confirm if all documents are available. The RI-HCor / BCRI will make the outcome CRF available and will include additional information in the complete package for the committee.

BCRI will forward two copies of each outcome package to the committee that will draw two independent physician reviewers. These physicians will independently review the cases, document and provide supporting information for each adjudication event. If both adjudicators agree, the event validation is considered complete. If there is disagreement between the reviewers or at the physician reviewer discretion, the case will be submitted to review of at least one additional reviewer to establish the final validation. The final adjudication result will be in the database by the committee coordinator. One copy of each signed adjudication form will be filed in the respective folder and will be stored by the committee. Additional details on the specific process for each one of the 2 committees groups will be separately informed in standard operating procedure documentation between HCor and BCRI.

All adjudications will be documented in the review package, respecting the established outcome criterion. For any case that gives precedence, the Committee Coordinator will document the adjudication details, and the case will be registered in a log which will serve as a guide for the reviewers in order to be consistent with the application of the outcome definitions.

8.5 Data Quality Management and Maintenance

Several procedures that guarantee data quality and protocol standardization will also contribute to minimize bias. Such procedures include: 1) an one-day training will be given to all Research Coordinators before study initiation, to guarantee consistency with study procedures; 2) a detailed Operations Manual of the SECURE-PCI Trial will describe each protocol step; 3) the project coordinator will accompany the visits to the participating sites to review protocol and to give new training, as necessary; 4) an electronic data capture system will identify point data validation, questions or corrections if errors are detected during quality control verifications; and 5) the Coordinator Site will prepare detailed monthly reports on screening, recruitment, randomization, data quality, protocol adherence, consistency and perfection of data collection, in addition to include event rates. The Coordinator Site team will be available every day to solve

possible problems and questions of the Research Coordinators and Investigators from the Participant Sites.

In addition, because this is a pragmatic study (large simple trial), the study CRFs are concise and focused on essential clinical data that would be collected as part of the daily clinical practice. In this way, the SECURE-PCI Trial does not require any extra workload from the participating physicians in terms of patient management and follow up, thus minimizing the possibility of errors, missing data, and potentially maximizing recruitment rates.

8.6 Study Sponsor Responsibilities

This is a relevant clinical research, designed and sponsored by HCor Research Institute - RI-HCor and BCRI, both academic clinical research organizations, based in São Paulo, Brazil. The aim of the study is exclusively to obtain the best scientific knowledge on daily clinical practice, free of any conflicts of interest with the pharmaceutical industry. In this sense, possible sponsors will not have any participation role in the Steering Committee, in protocol writing, in data analysis, in making decision about study procedures or in the preparation of study publications, if appropriate, it will be mentioned as source of financial study support in presentations and publications. The SECURE-PCI Trial will be published independently of the results found, whether positive or negative.

8.7 Investigators and Co-investigators Responsibilities at Participant Sites

The Principal Investigator (PI) of each site will conduct and/or supervise the daily project operations at their participant site, along with Co-investigators and Research Coordinators. Most tasks can be delegated by the principal investigator to the site's research professionals; provided these professionals are qualified for the tasks and these delegations are registered including the professional's name and their respective position. However, the legal responsibility remains with the Principal Investigator. In addition, the investigators' attributions are initiating the study at their sites, its maintenance, guaranteeing protocol improvement, as well as data quality and veracity.

9 RESULTS PUBLICATION

The success of SECURE-PCI Trial will depend on the research team involved, on the efforts and collaboration of all investigators, research coordinators and patients. Therefore, the main results

will be published having as authors the professional team that had participated in the study (not only the study organizers).

10 PROTOCOL AMENDMENTS

Any protocol modification agreed will be recorded in writing via an amendment signed by the principal investigator.

The IRB approval and recommendation of the changes are required before their implementation, unless there are reasons that superimpose such approval or recommendation.

In some cases, an amendment can require changes to the informed consent form. The Investigator must receive the approval or recommendation of the revised form before implementing the changes. Besides, changes to the CRFs, if required, will be incorporated in the amendment. Before proceeding with the changes, the protocol amendment must be submitted to the Regulatory Authorities, if applicable, except in emergency situations.

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APPENDIX 1

Guidance in special situations:

According to different clinical situations observed during the study and preserving the intention to treat principle, the following actions were established:

1) All randomized patient, who received the study drug, but **WITHOUT indication** of percutaneous coronary approach, however with known coronary disease or intermediate or high cardiac risk **OR** when the coronary angioplasty is postponed for **more than 7 days** after the onset date of the acute coronary syndrome (ACS), should be followed by intention to treat with 30-day follow up (IN PERSON, WITH LABORATORY EXAMS COLLECTION), 6-month and 12-month. The second dose of study drug as well as the maintenance doses and the statin prescription to these patients will be at the responsible physician discretion (recommended in cases of angiography with evidence of coronary artery disease).

2) All randomized patient, who received study drug, who met eligibility criteria, but who have **NOT** had the acute coronary syndrome confirmation and with **low cardiac risk** should be followed by intention to treat with 30-day, 6-month and 12-month follow up, being allowed the phone contact. The second dose of study drug and maintenance statin should be done at the physician discretion.

3) For all randomized patient, who received study drug and who have not undergone coronary angioplasty, the occurrence of a new acute myocardial infarction with indication of percutaneous approach, should be considered as a clinical outcome, being **FORBIDDEN** the inclusion of patients already randomized in the study.

4) All patient included in the study with delay in performing percutaneous coronary angioplasty (within 1-7 days after ACS presentation), if indicated and at the physician discretion, may receive statin and/or fibrate in open label provided it does not exceed the maximum dose allowed by the study in the 24 hours prior to the percutaneous procedure. In these situations that the patient was randomized, took the loading study dose, but the angioplasty was postponed beyond 24 hours, however within the 7 days

of ACS: When angioplasty is rescheduled, patient should receive the pre-procedure loading dose (contingency drug), undergo the angioplasty, receive the booster dose 24 hours after the procedure and initiate maintenance statin on the next day after the day that received the booster.